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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,393	12/26/2006	Wolfgang Kranewitter	GRE-106us	1617

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EXAMINER	
WOOLWINE, SAMUEL C	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
03/22/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,393	KRANEWITTER ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30 and 70-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30 and 70-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 January 2011* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's response filed 01/05/2011 is acknowledged. Claims 29, 30, and 70-95 are pending in the application.

The objection to the drawings made in the previous Office action is withdrawn in view of the replacement drawings submitted with the response.

The objection to claims 29 and 87 as being in improper Markush form is withdrawn in view of the amendment.

The rejection of claims 30, 71, 73, 76, 79, 82 and 85 under 35 USC 112, 2nd paragraph is withdrawn in view of the amendment.

The rejection of claims 30, 71, 73, 76, 79, 82 and 85 under 35 USC 112, 1st paragraph is withdrawn in view of the amendment.

The rejections of claims 29, 30, and 70-95 under 35 USC 103 made in the Office action mailed 07/06/2010 are maintained for the reasons of record.

Response to Arguments

Applicant's arguments filed 01/05/2011 have been fully considered but they are not persuasive. After citing relevant case law and the requirements for a *prima facie* case of obviousness (section V of the response), it is noted that Applicant does not specifically point out any particular shortcoming (e.g. rationale to combine, reasonable expectation of success, etc). Applicant merely asserts that "neither Thunnissen et al., nor any of the other cited prior art, disclose, suggest or otherwise render obvious the claimed nucleotide array". The Applicant does not argue that the rationale pointed out

by the Examiner was either lacking or improper. To summarize, the rationale was that one of ordinary skill in the art would have understood that alternative regions of the E1 gene to those actually used by Thunnissen would have been obvious in light of that artisans teachings of identifying HPV genotypes based on differences in the E1 gene, and the fact that the sequences of the E1 gene for numerous HPV genotypes were known.

Rather, Applicant's sole argument for non-obviousness is based on an allegation that "the probes of claim 29 produce unexpectedly advantageous results". This allegation, in turn, is based on the fact that in some cases, integration of an HPV genome into the host genome is accompanied by deletion of various parts of the HPV genome. In particular, Applicant cites Doorbar (2005), which discloses that in the case of high risk HPV types, the viral E2 and E4 genes are often lost (page S13, left column). Applicant reasons that, since the E2 gene lies 3' of the E1 gene (in fact, the 5' end of the former often overlapping the 3' end of the latter), the loss of E2 "very likely also leads to a deletion of the 3' -end of the neighboring E1 gene". Applicant concludes that, since the probes/primers of the invention are further 5' in the E1 gene than are Thunnissen's, they would be more reliable since in some cases the portion of the E1 gene to which Thunnissen's primers/probes correspond would be lost.

This line of argument is not persuasive for a number of reasons. First and foremost, Applicant is alleging that the primers/probes of the invention produce "unexpectedly advantageous results". However, Applicant has submitted no evidence whatsoever that this is the case. Applicant merely argues a reason why the

primers/probes of the invention *might* be more reliable. Unexpected properties, to be persuasive, must be demonstrated by evidence.

Second, in order for unexpected properties to confer patentability on otherwise obvious claims, the claims must be commensurate in scope with the claimed invention. The aspect of loss of the E2 (and E1) HPV genes appears to occur in the context of carcinogenesis. However, not all of the HPV genotypes corresponding to the SEQ ID NOs recited in the claims are of the carcinogenic (or high-risk) type.

Third, unexpected properties must actually be unexpected. It was known in the prior art that portions of the E2 and/or E1 genes could be lost from the integrated genomes of high-risk HPV types. For instance, Kalantari et al (1998) mapped areas of deletions of the E1 and E2 genes using PCR. The found that of 158 cervical carcinoma samples tested, 23% showed no amplification with primers designed to amplify E1, while 29% showed no amplification with primers designed to amplify E2 (abstract). There was some, but not complete, overlap between the samples negative for E1 and E2 (*id.*). This agrees with Applicant's position that, in some cases where a portion of E2 is lost, a portion of E1 is lost as well. Importantly, however, Kalantari found that of 35 samples negative for E1, 11 were positive in specific amplification of the 3' end of the E1 gene (*id.*). It follows, then, that for these samples, the deletion was not in the 3' end of E1, but in portions 5' thereof. What this all goes to show is that (1) it would not have been unexpected that Thunnissen's primers/probes would fail in some cases when a deletion of the 3' end of E1 had occurred, (2) that primers/probes to portions 5' of the 3' end of the E1 gene would fail in some cases when a deletion in a 5' region of the E1

gene had occurred. That is, the fact that deletions occur sometimes in the 3' region of E1 and sometimes in the 5' region of E1 undermines the argument that 5' primers/probes are more reliable than 3' primers/probes.

Likewise, Chen et al (1994) analyzed HPV16 integration in cervical cancer samples and found "[a] general deletion domain of 1,465 bp in the integrated viral genome has been defined between nt 1417-2881, covering most of the E1 ORF at the 3'-half and 60 bp at the 5' terminus of the E2 ORF" (abstract). It is noted that, according to Applicant, "amplification primers of the present invention...cover a region from 2056 to 2402" according to the HPV16 genome. This places the amplification primer of the present invention squarely within the general deletion domain described by Chen. Again, this undermines Applicant's position that the primers/probes of the invention are more reliable than Thunnissen's.

Because Applicant has not actually demonstrated the primers/probes of the invention to have unexpectedly advantageous properties, and because it would have been expected that in some cases of integration of HPV, viral genomic loss would result in failure of primers/probes to the E1 gene whether in the 5' or the 3' region, and finally because the claims are not commensurate in scope with the alleged unexpected properties, Applicant's arguments are not persuasive and the rejections under section 103 made in the Office action mailed 07/06/2010 are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Primary Examiner